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ance Notes on Codes and Abbreviations" appearing at the begin-  
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(54) Title: PIPERIDINE-DERIVATIVES AS PDE4 INHIBITORS

(57) Abstract: The compounds of a certain formula (1), in which the given substituents have the meanings as indicated in the description, are novel effective PDE4 inhibitors.



**WO 2004/018449 A1**

## PIPERIDINE-DERIVATIVES AS PDE4 INHIBITORS

**Field of application of the invention**

The invention relates to novel piperidine derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

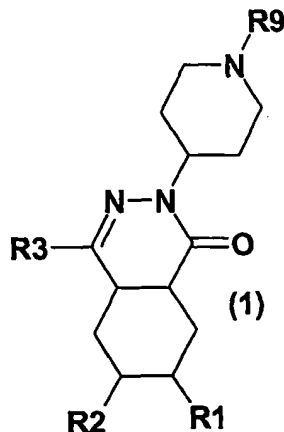
**Known technical background**

International Patent Applications WO98/31674 (= USP 6,103,718), WO99/31071, WO99/31090, WO99/47505 (= USP 6,255,303), WO01/19818, WO01/30766, WO01/30777, WO01/94319, WO02/064584, WO02/085885 and WO02/085906 disclose phthalazinone derivatives having PDE4 inhibitory properties. In the International Patent Application WO94/12461 and in the European Patent Application EP 0 763 534 3-aryl-pyridazin-6-one and arylalkyl-diazinone derivatives are described as selective PDE4 inhibitors. International Patent Application WO93/07146 (= USP 5,716,954) discloses benzo and pyrido pyridazinone and pyridazinthione compounds with PDE4 inhibiting activity.

In the Journal of Medicinal Chemistry, Vol. 33, No. 6, 1990, pp. 1735-1741 1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene derivatives are described as potent phosphodiesterase inhibitors and inodilators. In the Journal of Medicinal Chemistry Vol. 45 No.12, 2002, pp. 2520-2525, 2526-2533 and in Vol. 44, No. 16, 2001, pp. 2511-2522 and pp. 2523-2535 phthalazinone derivatives are described as selective PDE4 inhibitors.

**Description of the invention**

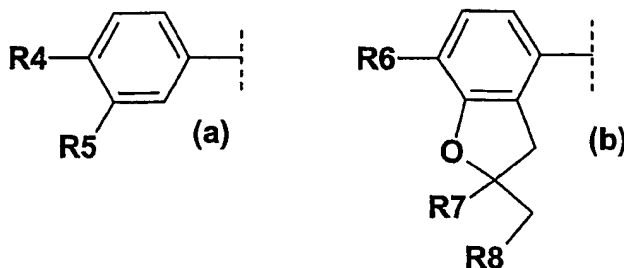
It has now been found that the piperidine derivatives, which are described in greater details below, have surprising and particularly advantageous properties. The invention thus relates to compounds of formula 1



in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, aryl-1-4C-alkyl, aryl-1-4C-alkyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenyl-1-4C-alkyl substituted by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophen-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R13 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R14 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R15 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R16 is hydrogen or halogen,

- R17 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R18 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R19 is hydrogen or halogen,
- R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R21 is hydrogen, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R22 is hydrogen or halogen,
- Aryl is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromalyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- and the salts of these compounds.

If R1 and R2 together are an additional bond, then the carbon atoms in the position 6 and 7 in the hexahydro-phthalazinone ring system of the compounds of formula 1 are linked to one another via a double bond (-> tetrahydrophthalazinone ring system).

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

1-8C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Alkoxy radicals having 1 to 8 carbon atoms which may be mentioned in this context are, for example, the octyloxy, heptyloxy, isoheptyloxy (5-methylhexyloxy), hexyloxy, isohexyloxy (4-methylpentyloxy), neohexyloxy (3,3-dimethylbutoxy), pentyloxy, isopentyloxy (3-methylbutoxy), neopentyloxy (2,2-dimethylpropoxy), butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

3-7C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy or cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-5C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy and cyclopentyloxy.

3-5C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

As spiro-linked 5-, 6- or 7-membered hydrocarbon rings, optionally interrupted by an oxygen or sulphur atom, may be mentioned the cyclopentane, cyclohexane, cycloheptane, tetrahydrofuran, tetrahydropyran and the tetrahydrothiophen ring.

Halogen within the meaning of the present invention is bromine, chlorine or fluorine.

1-4C-Alkoxy carbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl [ $\text{CH}_3\text{O}-\text{C}(\text{O})-$ ] and the ethoxycarbonyl [ $\text{CH}_3\text{CH}_2\text{O}-\text{C}(\text{O})-$ ] radical.

An 1-4C-Alkylcarbonylamino radical is, for example, the propionylamino [ $\text{C}_3\text{H}_7\text{C}(\text{O})\text{NH}-$ ] and the acetyl amino radical [ $\text{CH}_3\text{C}(\text{O})\text{NH}-$ ].

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

Phenyl-1-4C-alkyl radicals stand for one of the abovementioned 1-4C-alkyl radicals substituted by an phenyl group. Examples which may be mentioned are the phenylethyl and the benzyl radical.

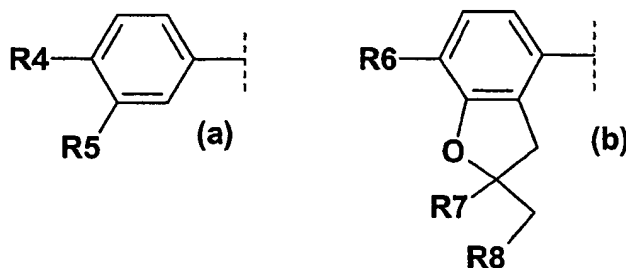
Aryl-1-4C-alkyl radicals stand for one of the abovementioned 1-4C-alkyl radicals substituted by an Aryl group. Examples which may be mentioned are the pyrid-3-ylmethyl and the pyrid-4-ylmethyl radical.

Suitable salts for compounds of the formula 1 are all acid addition salts. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula 1 as well as all solvates and in particular all hydrates of the salts of the compounds of formula 1.

Compounds of formula 1 to be emphasized are those in which  
R1 and R2 are both hydrogen or together form an additional bond,  
R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13, phenylethyl, benzyl, benzyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, arylmethyl, arylmethyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenylmethyl substituted in the naphthalenyl moiety by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophen-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,

R13 is hydrogen or halogen,

R14 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,

R15 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R16 is hydrogen or halogen,

R17 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl,

R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,

R21 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R22 is hydrogen or halogen,

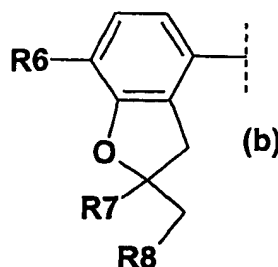
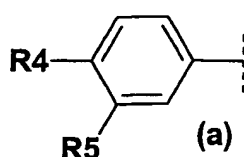
Aryl is pyridinyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

and the salts of these compounds.

Preferred compounds of formula 1 are those, in which

R1 and R2 together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



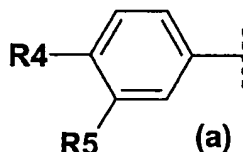
wherein

- R4 is 1-2C-alkoxy,
  - R5 is 1-4C-alkoxy,
  - R6 is 1-2C-alkoxy,
  - R7 is methyl and
  - R8 is hydrogen,
  - R9 is  $-S(O)_2-R_{10}$ ,
  - R10 is phenyl substituted by R11, benzyl, aryl, aryl substituted by R17, R18 and R19, naphthalenyl, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,
  - R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
  - R17 is halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxycarbonyl,
  - R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
  - R19 is hydrogen or halogen,
  - Aryl is pyridinyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- and the salts of these compounds.

Particularly preferred compounds of formula 1 are those in which

R1 and R2 together form an additional bond,

R3 represents a phenyl derivative of formula (a)

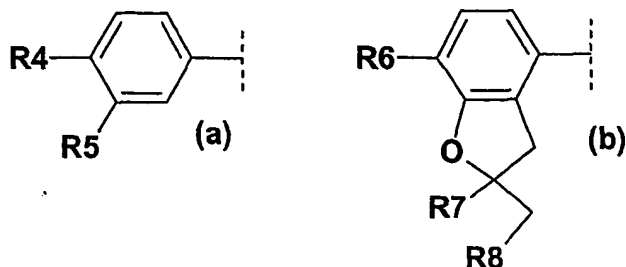


wherein

- R4 is methoxy,
  - R5 is methoxy,
  - R9 is naphthalene-1-sulfonyl, phenylmethanesulfonyl, 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl, quinolin-8-sulfonyl, thiophene-2-sulfonyl, 3,5-dimethyl-isoxazole-4-sulfonyl, 5-chloro-thiophene-2-sulfonyl, 2-trifluoromethoxybenzene-2-sulfonyl, 3-methoxy-4-methoxycarbonyl-thiophene-2-sulfonyl, 4-benzenesulfonyl-thiophene-2-sulfonyl, 5-(phenylcarbonylaminomethyl)thiophene-2-sulfonyl, 5-isoxazol-3-yl-thiophene-2-sulfonyl, 4,5-dichloro-thiophene-2-sulfonyl, 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl, 5-pyridin-2-yl-thiophene-2-sulfonyl or 4-trifluoromethoxybenzene-2-sulfonyl,
- and the salts of these compounds.



An embodiment (embodiment A) of the compounds of formula 1 are those in which  
 R1 and R2 are both hydrogen or together form an additional bond,  
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, aryl-1-4C-alkyl, aryl-1-4C-alkyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenyl-1-4C-alkyl substituted by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminoethyl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R13 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R14 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R15 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R16 is hydrogen or halogen,

R17 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R18 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R21 is hydrogen, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R22 is hydrogen or halogen,

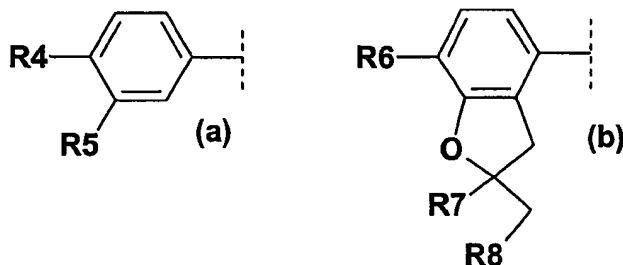
Aryl is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromalyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

and the salts of these compounds.

Compounds of formula 1 of embodiment A, which are to be emphasized are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

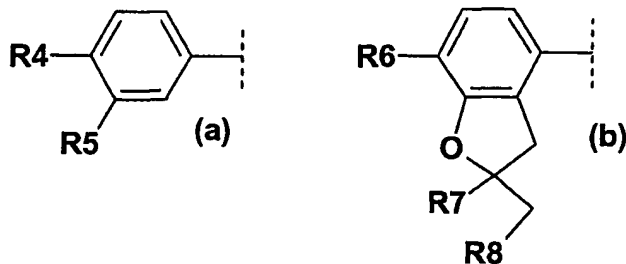
R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R9 is  $-S(O)_2-R_{10}$ ,

- R10 is phenyl substituted by R11, R12 and R13, phenylethyl, benzyl, benzyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, arylmethyl, arylmethyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenylmethyl substituted in the naphthalenyl moiety by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,
- R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
- R12 is hydrogen, halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,
- R13 is hydrogen or halogen,
- R14 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,
- R15 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
- R16 is hydrogen or halogen,
- R17 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl,
- R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
- R19 is hydrogen or halogen,
- R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,
- R21 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
- R22 is hydrogen or halogen,
- Aryl is pyridinyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- and the salts of these compounds.

Compounds of formula 1 of embodiment A, which are particularly to be emphasized are those in which R1 and R2 together form an additional bond,

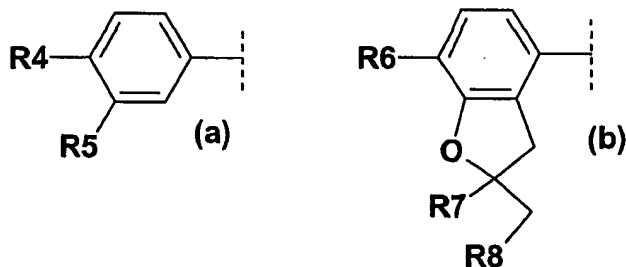
R3 represents a phenyl derivative of formulae (a) or (b)



wherein

- R4 is 1-2C-alkoxy,  
 R5 is 1-4C-alkoxy,  
 R6 is 1-2C-alkoxy,  
 R7 is methyl and  
 R8 is hydrogen,  
 R9 is  $-S(O)_2-R_{10}$ ,  
 R10 is phenyl substituted by R11, benzyl, aryl, aryl substituted by R17, R18 and R19, naphthalenyl, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,  
 R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,  
 R17 is halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxycarbonyl,  
 R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,  
 R19 is hydrogen or halogen,  
 Aryl is pyridinyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,  
 and the salts of these compounds.

Another embodiment (embodiment B) of the compounds of formula 1 are those in which  
 R1 and R2 are both hydrogen or together form an additional bond,  
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

- R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,  
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,  
 R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,  
 R7 is 1-4C-alkyl and  
 R8 is hydrogen or 1-4C-alkyl,  
 or wherein  
 R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-S(O)_2-R_{10}$ ,

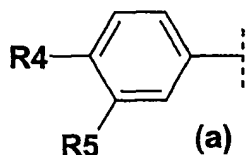
R10 is phenyl substituted by R11, R12 and R13,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R13 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,  
and the salts of these compounds.

Compounds of formula 1 of embodiment B, which are to be emphasized are those in which  
R1 and R2 together form an additional bond,  
R3 represents a phenyl derivative of formula (a)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13,

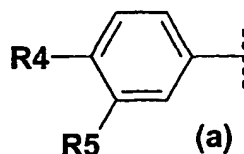
R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R13 is hydrogen,

and the salts of these compounds.

Compounds of formula 1 of embodiment B, which are particularly to be emphasized are those in which  
R1 and R2 together form an additional bond,  
R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

R5 is methoxy,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13,

R11 is trifluoromethoxy,

R12 is hydrogen,

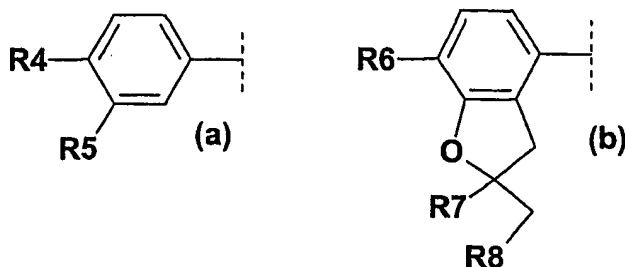
R13 is hydrogen,

and the salts of these compounds.

A further embodiment (embodiment C) of the compounds of formula 1 are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-S(O)_2-R10$ ,

R10 is aryl, aryl substituted by R17, R18 and R19, aryl-1-4C-alkyl, aryl-1-4C-alkyl substituted in the aryl moiety by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,

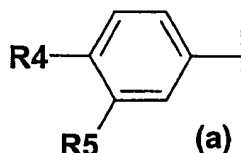
R17 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R18 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

Aryl is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxaliny, cinnoliny, quinoly, isoquinoly, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromalyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl, and the salts of these compounds.

Compounds of formula 1 of embodiment C which are to be emphasized are those in which R1 and R2 together form an additional bond, R3 represents a phenyl derivative of formula (a)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is aryl, aryl substituted by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophen-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,

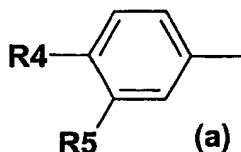
R17 is halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxycarbonyl,

R18 is hydrogen; halogen, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen,

Aryl is quinolyl, isoquinolyl, benzofuranyl, benzothiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl, and the salts of these compounds.

Compounds of formula 1 of embodiment C which are particularly to be emphasized are those in which R1 and R2 together form an additional bond, R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

R5 is methoxy,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is aryl, aryl substituted by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,

R17 is halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxycarbonyl,

R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

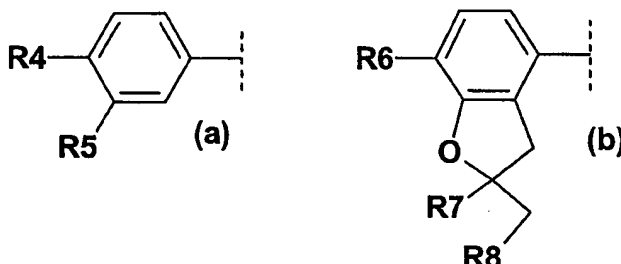
R19 is hydrogen,

Aryl is quinolyl, benzothiophenyl, isoxazolyl, pyrazolyl or thiophenyl, and the salts of these compounds.

Still a further embodiment (embodiment D) of the compounds of formula 1 are those in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-S(O)_2-R10$ ,

R10 is phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R14, R15 and R16, naphthalenyl, naphthalenyl substituted by R20, R21 and R22 or naphthalenyl-1-4C-alkyl substituted by R17, R18 and R19,

R14 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R15 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,



R16 is hydrogen or halogen,

R17 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R18 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

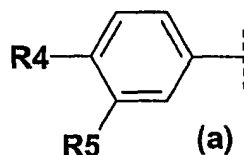
R19 is hydrogen or halogen,

and the salts of these compounds.

Compounds of formula 1 of embodiment D which are to be emphasized are those in which

R1 and R2 together form an additional bond,

R3 represents a phenyl derivative of formula (a)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is benzyl, benzyl substituted in the phenyl moiety by R14, R15 and R16, naphthalenyl or naphthalenyl substituted by R20, R21 and R22,

R14 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R15 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R16 is hydrogen,

R20 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R21 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

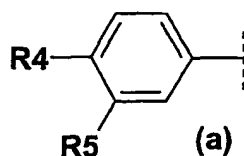
R22 is hydrogen,

and the salts of these compounds.

Compounds of formula 1 of embodiment D which are to be emphasized are those in which

R1 and R2 together form an additional bond,

R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,  
 R5 is methoxy,  
 R9 is  $-\text{S}(\text{O})_2\text{-R}_{10}$ ,  
 R10 is benzyl or naphthalenyl,  
 and the salts of these compounds.

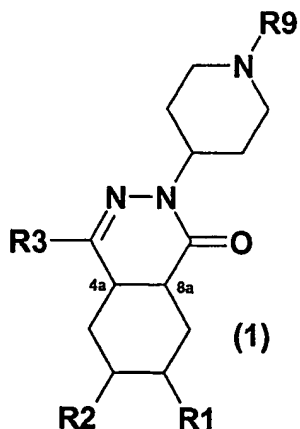
A special embodiment of the compounds of the present invention include those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a).

Another special embodiment of the compounds of the present invention include those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a) and R4 and R5 have the meaning methoxy.

Still another special embodiment of the compounds of the present invention include those compounds of formula 1 in which R1 and R2 together form an additional bond, R3 represents a phenyl derivative of formula (a) and R4 and R5 have the meaning methoxy.

The compounds of formula 1 are chiral compounds. Chiral centers exist in the compounds of formula 1 in the positions 4a and 8a. In case R3 represents a phenyl derivative of formula (b) there is one further chiral center in the dihydrofuran-ring, if the substituents -R7 and  $-\text{CH}_2\text{R}_8$  are not identical. However, preferred are in this connection those compounds, in which the substituents -R7 and  $-\text{CH}_2\text{R}_8$  are identical or together and with inclusion of the two carbon atoms to which they are bonded form a spiro-connected 5-, 6- or 7-membered hydrocarbon ring.

**Numbering:**

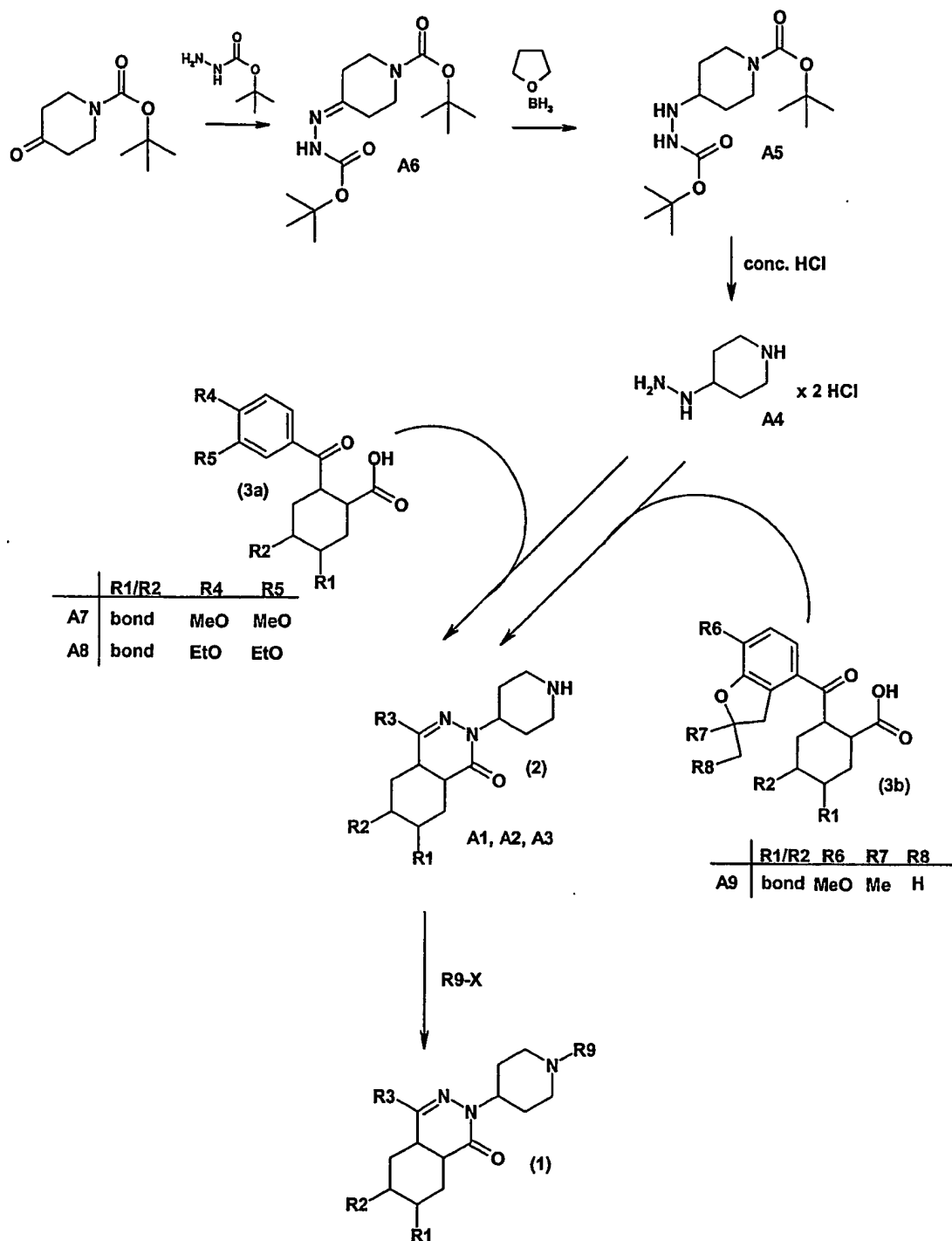


Therefore the invention includes all conceivable pure diastereomers and pure enantiomers of the compounds of formula 1, as well as all mixtures thereof independent from the ratio, including the racemates. Preferred are those compounds of formula 1, in which the hydrogen atoms in the positions 4a and 8a are cis-configured. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R

in the position 8a. Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers during the preparation with the help of an optical active separation agent on the stage of the cyclohexane-carboxylic acids or the 1,2,3,6-tetrahydrobenzoic acids (for example, starting compounds A7, A8 and A9). As separation agents may be mentioned, for example, optical active amines such as the (+)- and (-)-forms of 1-phenylethylamine [(R)-(+)-1-phenylethylamine = (R)-(+)- $\alpha$ -methylbenzylamine or (S)-(-)-1-phenylethylamine = (S)-(-)- $\alpha$ -methylbenzylamine) and ephedrine, the optical active alkaloids quinine, cinchonine, cinchonidine and brucine.

The compounds according to the invention can be prepared, for example, as described in Reaction scheme 1.

Reaction Scheme 1:



Reaction scheme 1 shows that the compounds of formula 1 can be, for example, prepared starting from 4-oxo-piperidine-1-carboxylic acid tert-butyl ester which is reacted in a first reaction step with tert-butylhydrazine to give 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A6). Compound A6 is reduced with, for example, the boran tetrahydrofuran com-

plex to give 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A5). Treatment of compound A5 with concentrated hydrochloric acid results in the formation of piperidin-4-yl-hydrazine dihydrochloride (starting compound A4).

The reaction of piperidin-4-yl-hydrazine dihydrochloride with cyclohexanecarboxylic acids or 1,2,3,6-tetrahydrobenzoic acids of formulae 3a or 3b leads to the piperidino derivatives of formula 2.

These are reacted in the final reaction step with compounds of formula R9-X, wherein X represents a suitable leaving group, preferably a chlorine atom, to give the compounds of formula 1.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallising the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula 1, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The following methods are used for characterizing the compounds: MS: atmospheric pressure chemical ionization mass spectrometry (APCI-MS). In the examples, h stands for hour(s), RT for room temperature and calc. for calculated.

The compounds mentioned in the examples and their salts are a preferred subject of the invention.

ExamplesFinal products

1. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(naphthalen-1-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

101.5 mg of (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride (starting compound A1) are dissolved in 5 ml dichloromethane and 161 µl of diisopropylethylamine are added. The solution is treated with 85 mg of naphthalene-1-sulfonyl chloride and the reaction mixture is stirred for 16 h. After evaporation the residue is purified by flash chromatography on silica to yield 72 mg of the title compound.

MS: calc: C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>S (559.69) found:[M+1] 560.2 HPLC[min]: 8.47

The following examples are prepared analogously to example 1:

2. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-(1-phenylmethanesulfonyl-piperidin-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>S (523.66) found:[M+1] 524.2 HPLC[min]: 8.13

3. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>26</sub>H<sub>32</sub>ClN<sub>5</sub>O<sub>5</sub>S (562.09) found:[M+1] 562.3 HPLC[min]: 7.64

4. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(quinoline-8-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>5</sub>S (560.68) found:[M+1] 561.3 HPLC[min]: 7.69

5. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> (515.65) found:[M+1] 516.2 HPLC[min]: 7.84

6. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(3,5-dimethyl-isoxazole-4-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S (528.63) found:[M+1] 529.2 HPLC[min]: 7.75

7. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(5-chloro-thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>25</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>5</sub>S<sub>2</sub> (550.1) found:[M+1] 550.1 HPLC[min]: 8.51

8. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(2-trifluoromethoxy-benzene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>28</sub>H<sub>30</sub>F<sub>3</sub>N<sub>3</sub>O<sub>6</sub>S (593.63) found:[M+1] 594.2 HPLC[min]: 8.52

9. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(3-methoxy-4-methoxycarbonyl-thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>O<sub>6</sub>S<sub>2</sub> (603.72) found:[M+1] 604.1 HPLC[min]: 8.01

10. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(4-benzenesulfonyl-thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>7</sub>S<sub>3</sub> (655.82) found:[M+1] 656.1 HPLC[min]: 8.48

11. N-(5-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

MS: calc: C<sub>33</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> (648.81) found:[M+1] 649.1 HPLC[min]: 7.83

12. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(5-isoxazol-3-yl-thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> (582.7) found:[M+1] 583.1 HPLC[min]: 8.13

13. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(4,5-dichloro-thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc: C<sub>25</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> (584.55) found:[M+1] 584.1 HPLC[min]: 8.97

14. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(5-chloro-3-methyl-benzof[b]thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc:  $C_{30}H_{32}ClN_3O_5S_2$  (614.19) found: [M+1] 614.1 HPLC[min]: 9.24

15. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc:  $C_{30}H_{32}N_4O_5S_2$  (592.74) found: [M+1] 593.2 HPLC[min]: 8.24

16. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(4-trifluoromethoxy-benzene-2-sulfonyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

MS: calc:  $C_{28}H_{30}F_3N_3O_6S$  (593.63) found: [M+1] 594.2 HPLC[min]: 8.67



**Starting Compounds and Intermediates****A1. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride**

A solution of 50 mmol of the salt of (S)-(-)- $\alpha$ -methylbenzylamine and (cis)-2-(3,4-dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A7), 55 mmol of piperidin-4-yl-hydrazine dihydrochloride and 100 mmol of triethylamine in 150 ml of 1-propanol is refluxed for 18 h. After cooling to RT, the precipitate is filtered off and dried. M. p. 285-288°C

**A2. (4aS,8aR)-4-(3,4-Diethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride**

Prepared from the salt of (S)-(-)- $\alpha$ -methylbenzylamine and (cis)-2-(3,4-diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A8) in 2-propanol as described for compound A1. M. p. 248-250°C

**A3. (cis)-4-(7-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride**

Prepared from (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4 carbonyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A9) in 1-propanol as described for compound A1. After evaporating the solvent, the residue is partitioned between dichloromethane and aqueous sodium carbonate. The dichloromethane layer is dried over magnesium sulfate and evaporated. The residue is dissolved in dichloromethane and after the addition of a solution of hydrochloric acid in ether, the compound precipitates. M. p. 288-290°C

**A4. Piperidin-4-yl-hydrazine dihydrochloride**

A mixture of 0.1 mole of 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A5) and 150 ml of concentrated hydrochloric acid is heated at 90°C for 60 min after which the clear solution is evaporated. The residue is washed with tetrahydrofuran, filtered off and dried under vacuum. M. p. 256-259°C

**A5. 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester**

150 ml of a solution of borohydride in tetrahydrofuran (1.0 mol/l) is slowly added to a solution of 0.12 mole of 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A6) in 100 ml of dry tetrahydrofuran. After complete addition, the mixture is stirred for another 30 min after which a 100 ml of water is added to destroy the excess of borohydride. Subsequently the

tetrahydrofuran is evaporated and the resulting aqueous solution extracted with diethyl ether. After drying the solvent over magnesium sulfate, the ether is evaporated. M. p. 112-115°C

**A6. 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester**

A mixture of 0.15 mole of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and 0.15 mole of tert-butylcarbazate in 250 ml of hexane is stirred for 18 h at RT. The precipitate is filtered off and dried under vacuum. M. p. 172-174°C

**A7. (cis)-2-(3,4-Dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid**

Prepared as described in WO98/31674.

**A8. (cis)-2-(3,4-diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid**

Prepared as described in WO99/47505.

**A9. (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-carbonyl)-1,2,3,6-tetrahydro-benzoic acid**

Prepared as described in WO99/31090.

**A10. (cis)-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentane-4-carbonyl)-cyclohexanecarboxylic acid**

Prepared as described in WO99/31090.

**Determination of HPLC-Values:**

A Superspher 60 RP-Select B 75 x 4 mm column from Merck was used; the chromatography was carried out at a column temperature of 40°C using a flow of 1 ml/min. The solvent system employed was solvent A (water) and solvent B (acetonitrile), with the following gradient course being used:

min	%A	%B
0.0	80	20
1.0	80	20
8.0	20	80
12.0	20	80
14.0	80	20
16.0	80	20

Detection was carried out by UV at 220 nm.

### Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alz-

heimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the above mentioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula 1 according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel for-

mers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10  $\mu\text{m}$ , advantageously of 2 to 6  $\mu\text{m}$ .

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the

active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

### **Biological Investigations**

The second messenger cyclic AMP (cAMP) is well-known for inhibiting inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H Tenor and C Schudt, in „Phosphodiesterase Inhibitors“, 21-40, „The Handbook of Immunopharmacology“, Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (JE Souness et al., Immunopharmacology 47: 127-162, 2000).

The antiinflammatory potential of PDE4 inhibitors in vivo in various animal models has been described (MM Teixeira, TIPS 18: 164-170, 1997). For the investigation of PDE4 inhibition on the cellular level (in vitro), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophilic (C Schudt et al., Arch Pharmacol 344: 682-690, 1991) or eosinophilic (A Hatzelmann et al., Brit J Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor- $\alpha$  in monocytes, macrophages or dendritic cells (Gantner et al., Brit J Pharmacol 121: 221-231, 1997, and Pulmonary Pharmacol Therap 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (DM Essayan, Biochem Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the afore-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

#### **Method for measuring inhibition of PDE4 activity**

PDE4 activity was determined as described by Thompson et al. (Adv Cycl Nucl Res 10: 69-92, 1979) with some modifications (Bauer and Schwabe, Naunyn-Schmiedeberg's Arch Pharmacol 311: 193-198, 1980). At a final assay volume of 200  $\mu$ l (96well microtiter plates) the assay mixture contained 20 mM Tris (pH 7.4), 5 mM  $MgCl_2$ , 0.5  $\mu$ M cAMP, [ $^3H$ ]cAMP (about 30,000 cpm/assay), the test compound and an aliquot of cytosol from human neutrophils which mainly contains PDE4 activity as described by Schudt et al. (Naunyn-Schmiedeberg's Arch Pharmacol 344: 682-690, 1991); the PDE3-specific inhibitor Motapizone (1  $\mu$ M) was included to suppress PDE3 activity originating from contaminating platelets. Serial dilutions of the compounds were prepared in DMSO and further diluted 1:100 (v/v) in the assays to obtain the desired final concentrations of the inhibitors at a DMSO concentration of 1 % (v/v) which by itself only slightly affected PDE4 activity.

After preincubation for 5 min at 37°C, the reaction was started by the addition of substrate (cAMP) and the assays were incubated for further 15 min at 37°C. 50  $\mu$ l of 0.2 N HCl was added to stop the reaction and the assays were left on ice for about 10 min. Following incubation with 25  $\mu$ g 5'-nucleotidase (Crotalus atrox snake venom) for 10 min at 37°C, the assays were loaded on QAE Sephadex A-25 (1 ml bed

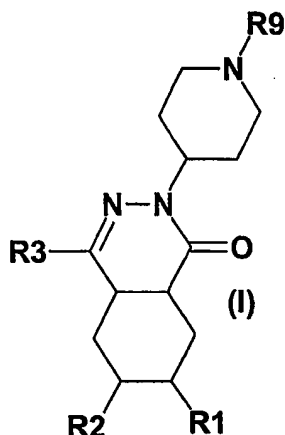


volume). The columns were eluted with 2 ml of 30 mM ammonium formate (pH 6.0) and the eluate was counted for radioactivity. Results were corrected for blank values (measured in the presence of denatured protein) which were below 5 % of total radioactivity. The amount of cyclic nucleotides hydrolyzed did not exceed 30 % of the original substrate concentration. The  $IC_{50}$ -values for the compounds according to the invention for the inhibition of the PDE4 activity were determined from the concentration-inhibition curves by nonlinear-regression.

The inhibitory values [measured as  $-\log IC_{50}$  (mol/l)] determined for the compounds 1 to 16 (the numbers of the compounds correspond to the numbers of the examples) according to the invention are all about 8.8 or greater.

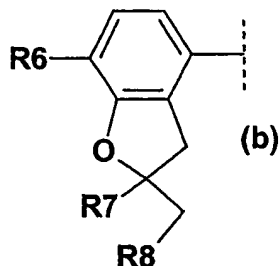
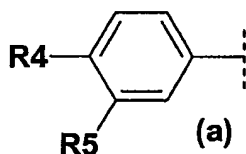
Patent claims

1. Compounds of formula 1,



in which

R1 and R2 are both hydrogen or together form an additional bond,  
R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

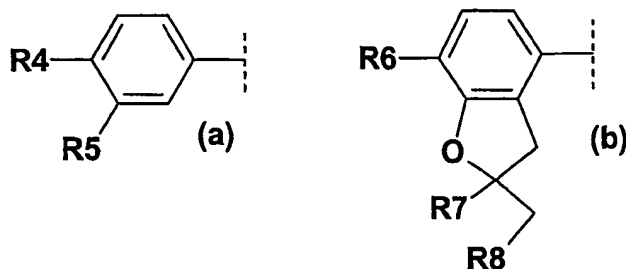
or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-\text{S}(\text{O})_2-\text{R}_{10}$ ,

- R10 is phenyl substituted by R11, R12 and R13, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, aryl-1-4C-alkyl, aryl-1-4C-alkyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenyl-1-4C-alkyl substituted by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,
- R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
- R12 is hydrogen, halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R13 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R14 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R15 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R16 is hydrogen or halogen,
- R17 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R18 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R19 is hydrogen or halogen,
- R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R21 is hydrogen, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R22 is hydrogen or halogen,
- Aryl is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromalyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- and the salts of these compounds.

2. Compounds of formula 1 according to claim 1, in which  
R1 and R2 are both hydrogen or together form an additional bond,  
R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13, phenylethyl, benzyl, benzyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, arylmethyl, arylmethyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenylmethyl substituted in the naphthalenyl moiety by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,

R13 is hydrogen or halogen,

R14 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,

R15 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R16 is hydrogen or halogen,

R17 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl,

R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

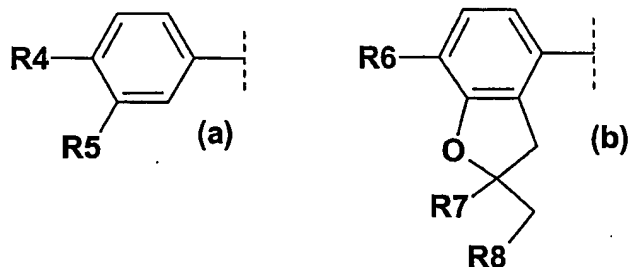
R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,

R21 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R22 is hydrogen or halogen,

Aryl is pyridinyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl, and the salts of these compounds.

3. Compounds of formula 1 according to claim 1, in which  
 R1 and R2 together form an additional bond,  
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, benzyl, aryl, aryl substituted by R17, R18 and R19, naphthalenyl, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl, 5-(pyridin-2-yl)thiophen-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R17 is halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxycarbonyl,

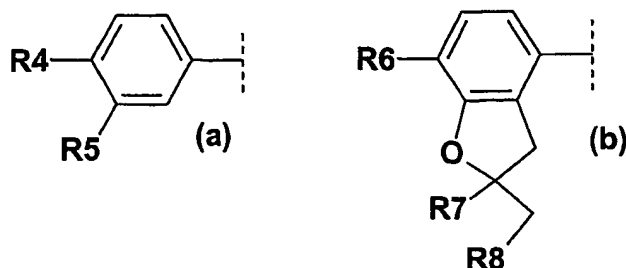
R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

Aryl is pyridinyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

and the salts of these compounds.

4. Compounds of formula 1 according to claim 1, in which  
 R1 and R2 are both hydrogen or together form an additional bond,  
 R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,  
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is  $-S(O)_2R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, aryl-1-4C-alkyl, aryl-1-4C-alkyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenyl-1-4C-alkyl substituted by R17, R18 and R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R12 is hydrogen, halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R13 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R14 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R15 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R16 is hydrogen or halogen,

R17 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or

di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R18 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R21 is hydrogen, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R22 is hydrogen or halogen,

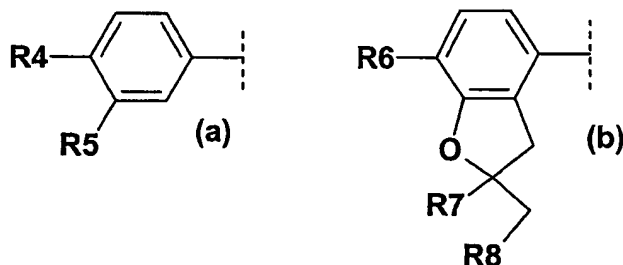
Aryl is pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

and the salts of these compounds.

5. Compounds of formula 1 according to claim 1, in which

R1 and R2 are both hydrogen or together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, R12 and R13, phenylethyl, benzyl, benzyl substituted in the phenyl moiety by R14, R15 and R16, aryl, aryl substituted by R17, R18 and R19, arylmethyl, arylmethyl substituted in the aryl moiety by R17, R18 and R19, naphthalenyl, naphthalenyl substituted by R20, R21 and R22, naphthalenylmethyl substituted in the naphthalenyl moiety by R17, R18 and

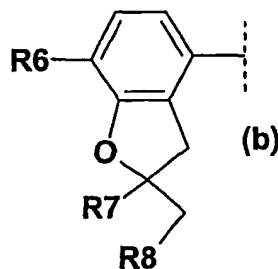
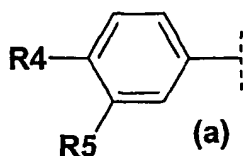
R19, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl or 5-isoxazol-3-yl-thiophen-2-yl,

- R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,  
 R12 is hydrogen, halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,  
 R13 is hydrogen or halogen,  
 R14 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,  
 R15 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,  
 R16 is hydrogen or halogen,  
 R17 is halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl,  
 R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,  
 R19 is hydrogen or halogen,  
 R20 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine or 1-4C-alkoxycarbonyl,  
 R21 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,  
 R22 is hydrogen or halogen,  
 Aryl is pyridinyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,  
 and the salts of these compounds.

6. Compounds of formula 1 according to claim 1, in which

R1 and R2 together form an additional bond,

R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and



R8 is hydrogen,

R9 is  $-S(O)_2-R_{10}$ ,

R10 is phenyl substituted by R11, benzyl, aryl, aryl substituted by R17, R18 and R19, naphthalenyl, 4-benzenesulfonyl-thiophene-2-yl, 5-(phenylcarbonylaminomethyl)thiophene-2-yl or 5-isoxazol-3-yl-thiophene-2-yl,

R11 is 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R17 is halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxycarbonyl,

R18 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R19 is hydrogen or halogen,

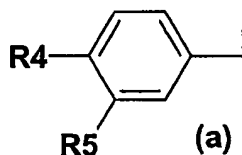
Aryl is pyridinyl, quinolyl, isoquinolyl, indolyl, indazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

and the salts of these compounds.

7. Compounds of formula 1 according to claim 1, in which

R1 and R2 together form an additional bond,

R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

R5 is methoxy,

R9 is naphthalene-1-sulfonyl, phenylmethanesulfonyl, 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl, quinolin-8-sulfonyl, thiophene-2-sulfonyl, 3,5-dimethyl-isoxazole-4-sulfonyl, 5-chloro-thiophene-2-sulfonyl, 2-trifluoromethoxybenzene-2-sulfonyl, 3-methoxy-4-methoxycarbonyl-thiophene-2-sulfonyl, 4-benzenesulfonyl-thiophene-2-sulfonyl, 5-(phenylcarbonylaminomethyl)thiophene-2-sulfonyl, 5-isoxazol-3-yl-thiophene-2-sulfonyl, 4,5-dichloro-thiophene-2-sulfonyl, 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl, 5-pyridin-2-yl-thiophene-2-sulfonyl or 4-trifluoromethoxybenzene-2-sulfonyl,

and the salts of these compounds.

8. Compounds of formula 1 according to one of the claims 1 to 7, in which the hydrogen atoms in the positions 4a and 8a are cis configured.

9. Compounds of formula 1 according to one of the claims 1 to 7, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.

10. Compounds of formula 1 according to claim 1 for the treatment of diseases.
11. Pharmaceutical compositions containing one or more compounds of formula 1 according to claim 1 together with the usual pharmaceutical auxiliaries and/or carrier materials.
12. Use of compounds of formula 1 according to claim 1 for the preparation of pharmaceutical compositions for the treatment of airway disorders.
13. A method for treating an illness treatable by administration of a PDE4 inhibitor in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.
14. A method for treating airway disorders in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08673

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 C07D401/14 C07D409/14 C07D413/14 A61K31/50  
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 064584 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 22 August 2002 (2002-08-22) page 25 -page 36; claims 1-13 ---	1-14
Y	WO 02 085906 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 31 October 2002 (2002-10-31) page 30 -page 38; claims 1-13 ---	1-14
Y	WO 01 30777 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 3 May 2001 (2001-05-03) cited in the application page 21 -page 25; claims 1-10 ---	1-14
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

29 October 2003

Date of mailing of the international search report

05/11/2003

Name and mailing address of the ISA

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Authorized officer

Kyriakakou, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08673

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 30766 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 3 May 2001 (2001-05-03) page 21 -page 25; claims 1-10 -----	1-14
Y	WO 01 19818 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 22 March 2001 (2001-03-22) cited in the application page 29 -page 33; claims 1-10 -----	1-14
Y	WO 99 47505 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 23 September 1999 (1999-09-23) cited in the application page 33 -page 37; claims 1-8 -----	1-14
Y	WO 99 31090 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 34 -page 38; claims 1-10 -----	1-14
Y	WO 99 31071 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 32 -page 36; claims 1-10 -----	1-14
Y	WO 98 31674 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 23 July 1998 (1998-07-23) cited in the application page 49 -page 55; claims 1-10 -----	1-14
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors. 3. In Vivo Antiinflammatory Activity of a New Series of N-Substituted cis-Tetra- and cis_hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2520-2525, XP002222828 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document -----	1-14
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARGARETHA VAN DER MEY ET AL.: "Novel selective Phosphodiesterase (PDE4) Inhibitors. 4. Resolution Configuration and PDE4 Inhibitory activity of cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2526-2533, XP002222829 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document	1-14
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 inhibitors. 1 Synthesis, Structure-Activity Relationships, and Molecular Modeling of 4-(3,4-Dimethoxyphenyl)-2H-phthalazin-1-ones and Analogues" JOURNAL OF MEDICINAL CHEMISTRY., vol. 44, no. 16, 2001, pages 2511-2522, XP002222830 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document	1-14
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 inhibitors. 2. Synthesis and structure-Activity Relationships of 4-Aryl-Substituted cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 44, no. 16, 2001, pages 2523-2535, XP002222831 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document	1-14

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/08673

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08673

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 02085906	A	31-10-2002	WO 02085906 A2	31-10-2002
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08673

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